Synthesis of New Polyfluoroalkyl-Containing Pyrones, Pyridones and Pyrido[1,2-*a*]benzazoles from Fluorinated β-Alkoxyenones

Nataliya A. Tolmachova,[a] Igor I. Gerus,*[a] Sergey I. Vdovenko,[a] Günter Haufe,*[b] Yuriy A. Kirzhner[c]

[a] Institute of Bioorganic Chemistry and Petrochemistry NASU, Murmanskaya 1, 03660 Kiev-94, Ukraine
Fax +38(044)5732552; E-mail: igerus@hotmail.com

[b] Organisch-Chemisches Institut, Universität Münster, Corrensstraße 40, 48149 Münster, Germany
Fax +49(251)8339772; E-mail: haufe@uni-muenster.de

[c] Enamine Ltd, A. Matrosova 23, 01103 Kiev, Ukraine
Fax +38(044)5373253; E-mail: nmr@enamine.net

Received 5 July 2007; revised 18 September 2007

Abstract: Fluorinated enones were reacted with thiazoles, imidazoles, benzimidazoles and benzthiazoles bearing methylene groups activated by electron-withdrawing substituents. The reactions start with a nucleophilic attack of the methylene carbon on the β-position of the enones. If the starting methylene compound contains a thiazole ring, pyrones or pyridones were formed due to participation of the ester or nitrile groups. In other cases, imidazo-, benzimidazo- or benzthiazo-pyridines were obtained by participation of the nitrogen atom of the corresponding azole rings. In addition to the final products, some primary products were isolated or proved as intermediates.

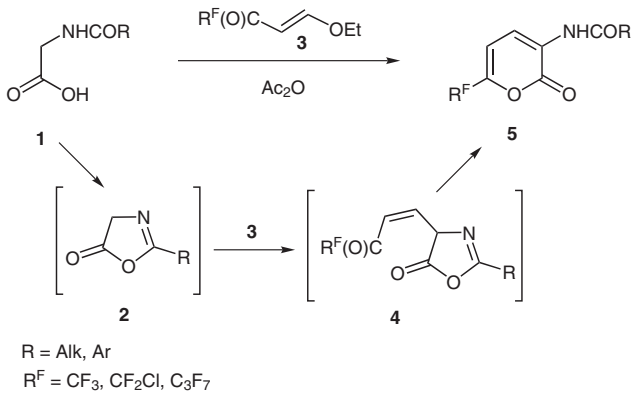
Key words: enones, heterocycles, pyridine, 2*H*-pyran-2-ones, polyfluoroalkyl group

The introduction of a polyfluoroalkyl group into organic molecules often confers significant and useful changes in their chemical and physical properties. Therefore, methods for the synthesis of polyfluoromethylated compounds have received considerable interest in recent years.[1] Pyridines, pyridones and pyrones are basic structural motifs found in numerous natural products having interesting properties for medicinal and agricultural applications. Molecules equipped with these scaffolds are known to exhibit diverse pharmacological activities as neuropeptide Y1 receptor antagonists,[2] muscle relaxants,[3] as antitumor,[4] antifungal,[5] and antiviral[6] agents, as free radical scavengers,[7] hypotensive[8] and cardiotropic[9] substances, and as inhibitors of voltage-dependent K^+ channels.[10]

Although direct polyfluoroalkylation is the most attractive and powerful tool with which to construct fluorinated compounds, polyfluoroalkyl-containing building blocks are often used as accessible and convenient starting materials. We systematically investigated the synthetic potential of readily available β-alkoxyvinyl polyfluoroalkyl ketones **3**, that may be considered as synthetic equivalents of polyfluoroacylacetaldehyde.[11] Numerous examples demonstrated the versatile synthetic applications of enones **3** in the synthesis of polyfluoroalkyl-containing heterocycles such as pyrimidines,[12] imidazopyridines,[13] pyrazoles and isoxazoles.[14]

Recently, we described an efficient synthesis of 3-acylamino-6-polyfluoroalkyl-2*H*-pyran-2-ones **5**,[15] by condensation of β-alkoxyvinyl polyfluoroalkyl ketones (enones) **3** and *N*-acylglycines **1** and its application in Diels–Alder reactions.[16]

As the first step of the reaction, we supposed the formation of intermediate oxazolones **2** from *N*-acylglycines **1** and acetic anhydride (Scheme 1). The oxazolones **2** have an active endocyclic methylene group, which subsequently undergoes a C–C coupling reaction with the enones **3**. However, we did not observe any reasonable quantity of intermediate oxazolones **4** in the reaction mixtures by ^{19}F NMR spectroscopy. In a continuation of our research on the synthesis of heterocyclic compounds, we have reacted the enones **3** with a range of active methylene compounds, such as various azoles bearing an exocyclic methylene group at position 2, activated by an electron-withdrawing group (EWG).

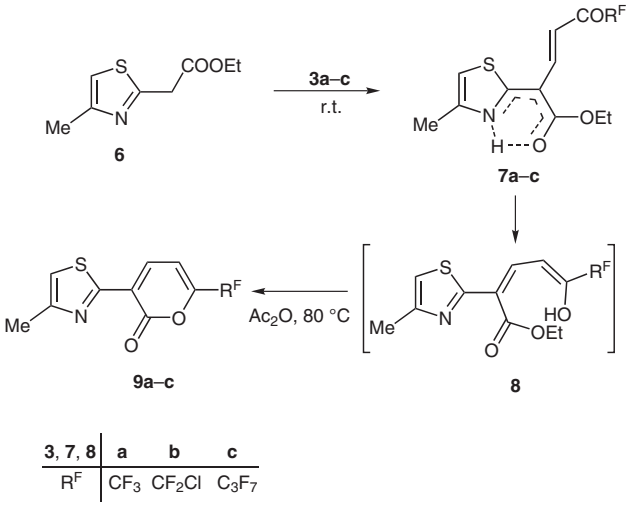


Scheme 1

Reactions of thiazole **6** with enones **3a–c** without a solvent, at room temperature, gave products **7** in good to high yields as a result of acylvinylation of the active methylene group (Scheme 2).

Products **7a–c** can exist in several tautomeric forms and we elucidated their structure by IR and NMR spectroscopy (Table 1 and Table 2). Thus, in the ^1H NMR spectra of

SYNTHESIS 2007, No. 24, pp 3797–3806
Advanced online publication: 15.11.2007
DOI: 10.1055/s-2007-990891; Art ID: T10207SS



3, 7, 8	a	b	c
R^F	CF_3	CF_2Cl	C_3F_7

Scheme 2

the products **7**, characteristic doublets of the vinyl protons at δ = 8.4 and 6.4 ppm with *trans*-vicinal coupling constants of 15–16 Hz and broad singlets arising from the NH protons at δ = 13.0–14.0 ppm were observed and the position of the hydrogen atom at the nitrogen was confirmed by NOE experiments for compound **7b** (Figure 1).

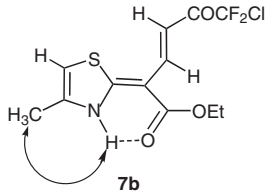
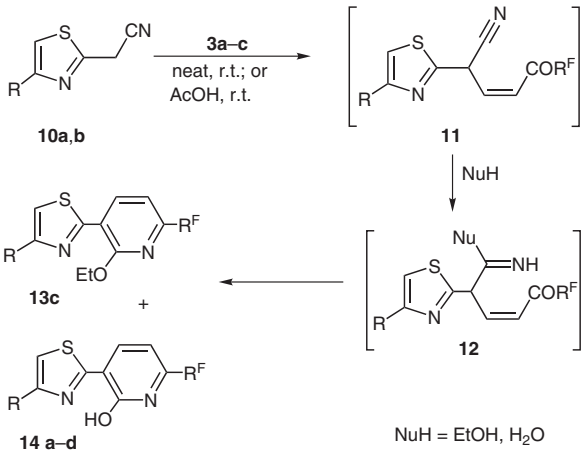


Figure 1 NOE-experiments for compound **7b**

Furthermore, in the IR spectra of products **7**, a broad absorption band of an intramolecular hydrogen bond was observed at 3670–2984 cm^{-1}. The data indicate that compounds **7** exist in tautomeric forms (Scheme 2), with an intramolecular hydrogen bond between the NH and C=O groups. A similar structure was suggested previously for a number of 2-thiazolylacetic esters.[17] We believe that, in contrast to intermediate oxazolones **4**, the intramolecular hydrogen bond sufficiently stabilizes compounds **7** to enable its separation and characterization.

Products **7** were cyclized to pyrones **9** by heating in acetic anhydride. Initially, compound **7** tautomerizes to intermediate **8**, followed by reaction of the enol and the ester groups with elimination of ethanol (Scheme 2). The structure of the synthesized pyrones **9** was confirmed by elemental analysis, IR and NMR spectroscopy (Tables 1 and Table 2). In the ^1H NMR spectra of compounds **9**, characteristic doublets of the protons at positions 5 and 4 of the pyrone ring at δ = 8.5 and 6.9 ppm, respectively, with a *cis*-vicinal coupling constant of 6–7 Hz were observed. Also in the IR spectra of products **9**, an intense absorption band of the carbonyl group was observed at 1672–1744 cm^{-1}.

The reaction of 1,3-thiazol-2-ylacetonitriles **10a** and **10b**, bearing a nitrile instead of the ester group in thiazole **6**, with enones **3a–c** at room temperature in acetic acid gave pyridines **14** in moderate to high yields (Scheme 3).



10	a	b
R	Me	Ph

11, 14	a	b	c	d
R^F	CF_3	CF_2Cl	C_3F_7	CF_3
R	Me	Me	Me	Ph

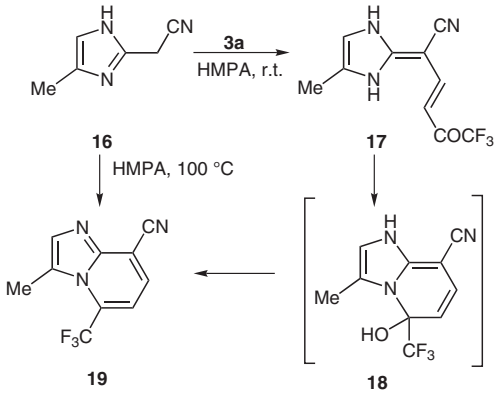
Scheme 3

According to the ^{19}F NMR spectra, the reaction mixtures contain 85–95% of the products **14**. The signals of polyfluoroalkyl groups of a main contaminant (5–15%) appeared at lower field. In the case of the reaction of the perfluoropropyl enone **3c**, we isolated the main contaminant (15% of the reaction mixture) by column chromatography. This compound was fully characterized by spectroscopic methods as the pyridine **13c**. Hence, we believe that the corresponding pyridines **13a**,**b**,**d** are also present in the product mixtures of the other reactions. The formation of the products **14** and **13** can be explained by competing nucleophilic addition of water or ethanol to the nitrile group, respectively. In contrast to the previous reactions of thiazole **6**, where compounds **7** were isolated, intermediates **11** were not detected by ^{19}F NMR spectroscopy in the reactions of thiazolylacetonitriles **10a** or **10b** with enones **3a–c** without a solvent at room temperature. The lability of intermediates **11**, compared to products **7**, is due to the higher reactivity of the nitrile group in heterocyclizations.[18]

The isolated products **13c** and **14a–d** gave satisfactory elemental analyses and spectroscopic data (IR, ^1H, ^{19}F and ^{13}C NMR) consistent with the assigned structures. For example, the IR spectra of products **13** and **14** did not show a nitrile absorption band near 2200 cm^{-1}, but compound **14** had a broad absorption band in the region 3450–3200 cm^{-1}. The NMR spectral data of the products **13c** and **14c** are very similar, allowing us to assign the structure of

compounds **14** as 2-hydroxypyridines rather than pyridin-2-ones in solution.

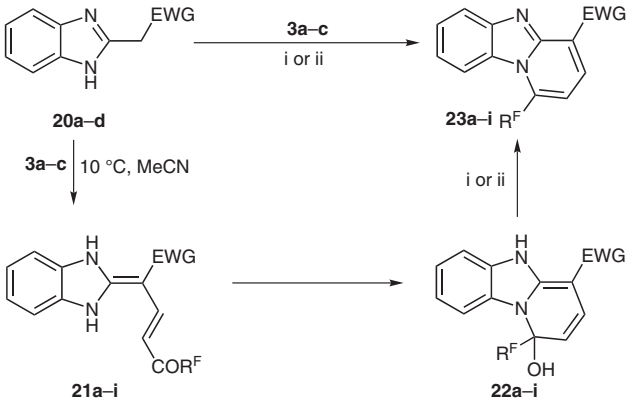
In contrast to the results of the reactions of 1,3-thiazol-2-ylacetonitriles **10** with enones **3**, the reaction between imidazole **16** and enone **3a** in hexamethylphosphoramide (HMPA) at 100 °C after 12 hours gave the product **19** as a result of cyclization by participation of the endocyclic nitrogen atom and the $COCF_3$ group, whereas the nitrile group remained untouched (Scheme 4). The structure of compound **19** was established on the basis of its NMR and IR spectroscopic data. In the IR spectrum, the nitrile absorption band at around 2200 cm^{-1} was still present. Under milder reaction conditions (in HMPA at r.t.), imidazole **16** gave intermediate compound **17**, whose structure was found to be similar to that of products **7**. Compound **17** was not stable at elevated temperature (see its broad melting-point range, Table 1), but cyclized to imidazopyridine **19** (indicated by TLC).



Scheme 4

In order to support our assumption of a specific role for the imidazole ring in the formation of pyridoimidazole **19** via intermediates **17** and **18**, we treated the benzimidazoles **20** with enones **3**. In these reactions the products were also formed by participation of the endocyclic nitrogen atom. Thus, heating of the benzimidazoles **20a–d** and enone **3a** in toluene or enone **3b** or **3c** in HMPA, gave pyrido[1,2-*a*]benzimidazoles **23** in high yields. Under milder reaction conditions (in acetonitrile at 10 °C) either compounds **21** (with EWG = CN) or **22** (with EWG = CO_2Me, COPh, $CONHCH_2Ph$) were formed. The products **23** were also obtained by heating compounds **21** or **22** (Scheme 5).

The nature of both the EWG and the polyfluoroalkyl groups play a crucial role in product formation. Substitution of one fluorine with a chlorine atom in the trifluoromethyl group leads to increased stability of the products **21e** and **22f**, which gave the corresponding pyridobenzimidazoles **23e** and **23f** only under forcing conditions (HMPA, 120 °C), compared to its trifluoromethyl analogues **21a** and **22b–d** (toluene, 110 °C). Moreover, the products **21h** and **22i**, bearing perfluoropropyl groups, are the most stable. Compound **21h** did not react even under



(i) 110 °C, toluene ($R^F = CF_3$), or (ii) 120 °C, HMPA ($R^F = CF_2Cl$, C_3F_7)

20	a	b	c	d
EWG	CN	COOMe	COPh	CONHBn

21–23	a	b	c	d	e	f	h	i
EWG	CN	COPh	COOMe	CONHBn	CN	COPh	CN	COPh
R^F	CF_3	CF_3	CF_3	CF_3	CF_2Cl	CF_2Cl	C_3F_7	C_3F_7

Scheme 5

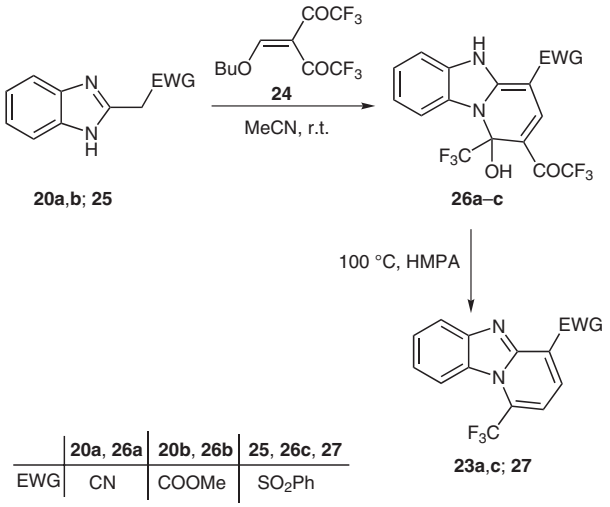
reflux in HMPA for one hour (assessed by TLC and ^{19}F NMR). The isolated products **21–23** have satisfactory elemental analyses and spectroscopic data (IR, ^1H, ^{13}C and ^{19}F NMR), which are consistent with the assigned structures.

Insertion of an electron-withdrawing substituent ($COCF_3$) in the α-position of the enone **3a**, enhances its reactivity and the bistrifluoroacetyl compound **24** reacted not only with benzimidazoles **20a** and **20b** but also with the sulfone **25**, which was unreactive towards enone **3a** in boiling toluene. Initially, ^{19}F NMR spectra of the reaction mixtures showed that compounds **26a–c** were formed. However, we only succeeded in isolating product **26b**, which is stabilized by two intramolecular hydrogen bonds. Its structure was confirmed by X-ray crystal structure analysis (Figure 2). The reaction of **20a**, **20b** and **25** with compound **24** under forcing conditions (HMPA, 100 °C) gave the products **23a**, **23c** and **27** as a result of elimination of trifluoroacetic acid (Scheme 6).

The products **26b** and **27** gave satisfactory elemental analyses and spectroscopic data (IR, ^1H, ^{13}C and ^{19}F NMR), which are consistent with the assigned structures. The NMR spectra of the products **23a** and **23c** were identical to those of the corresponding samples obtained from enone **3a**.

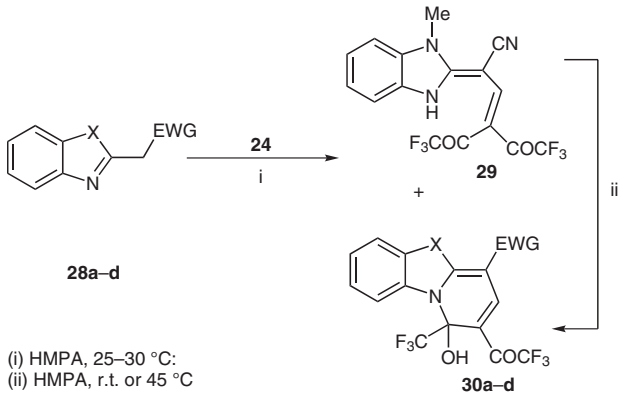
In contrast to enone **3a**, compound **24** reacted easily with benzthiazoles **28b–d** at room temperature to form products **30b–d** in high yields, whereas the chemical outcome of the reaction with *N*-methylbenzimidazole **28a** depended strongly on the temperature (Scheme 7).

While compound **30a** was formed as the sole product at 45 °C, an approximate 1:1 mixture of products **29** and **30**



	20a, 26a	20b, 26b	25, 26c, 27
EWG	CN	COOMe	SO_2Ph

Scheme 6



28,29,30	a	b	c	d
EWG	CN	CN	COPh	SO_2Ph
X	NMe	S	S	S

Scheme 7

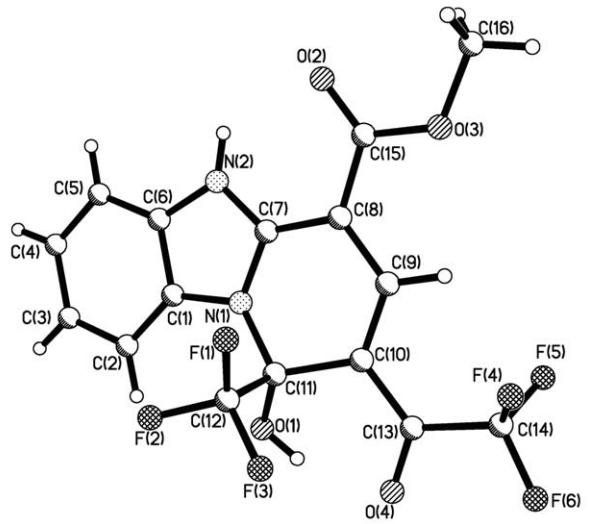


Figure 2 Crystal structure of methyl 1-hydroxy-2-(trifluoroacetyl)-1-(trifluoromethyl)-1,5-dihydropyrido[1,2-*a*]benzimidazole-4-carboxylate (**26b**).

was observed at room temperature (^{19}F NMR), and compound **29** was obtained as the main product at 10 °C. Initial formation of compound **29** was confirmed by its cyclization to highly pure product **30a** by stirring in HMPA at 25–30 °C. The products **29** and **30a–d** had satisfactory elemental analyses and spectroscopic data (IR, ^1H, ^{13}C and ^{19}F NMR), which are consistent with the assigned structures.

In summary, the chemical outcome of the reaction between fluorinated enones **3**, **24** and various heterocycles bearing a methylene group activated by an electron-withdrawing substituent, depends on the nature of the heterocyclic ring, the electron-withdrawing power of the polyfluoroalkyl groups and the reaction conditions.

In all cases, the reaction started with a nucleophilic attack of the methylene carbon atom on the β-position of the enones, followed by heterocyclization. In a number of cases, the initial intermediate products were isolated or observed spectroscopically. If a thiazole ring is in the starting methylene compounds, pyrones **9** or pyridones **14** were formed, owing to participation of the ester or nitrile groups, respectively. In other cases, imidazo- (**19**), benzimidazo- (**23**, **27**) or benzthiazo- (**30**) pyridines were obtained by participation of the nitrogen atom of the corresponding azole rings. High yields and simple preparation of the new polyfunctional compounds open a good possibility to use them as polyfluoroalkylated building blocks, particularly for the synthesis of biologically active compounds.

Melting points are uncorrected. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on Varian VXR (300 MHz), Varian Unian Plus (400 MHz) and Bruker Avance DRX (500 MHz) instruments, using TMS and CCl_3F as internal standards. IR spectra were recorded on a Specord M-80 spectrometer. Column chromatography was performed on silica gel 60 (Merck). Yields, physical constants and NMR data are shown in Table 1 and Table 2.

The following compounds were prepared by literature methods: 4-ethoxy-1,1,1-trifluorobut-3-en-2-one,[19] 1-chloro-4-ethoxy-1,1-difluorobut-3-en-2-one,[11b] 1-ethoxy-4,4,5,5,6,6,6-heptafluorohex-1-en-3-one,[11b] 3-ethoxymethylene-1,1,1,5,5,5-hexafluoropentane-2,4-dione.[20] All other reagents were obtained from usual commercial sources or Enamine Ltd. (Kiev). All solvents and liquid reagents were distilled before use.

Synthesis of Compounds 7a–c; General Procedure

A mixture of ethyl (4-methyl-1,3-thiazol-2-yl)acetate (**6**; 300 mg, 1.6 mmol) and enone **3a–c** (1.6 mmol) was heated in a tube with a Teflon-lined screw-cap at 60 °C for 0.5 h. The reaction mixture was stirred at r.t. overnight then the solid was treated with an Et_2O–hexane mixture (1:5), filtered, dried in air and crystallized (CCl_4).

Synthesis of Pyrones 9a–c; General Procedure

A solution of compound **7** (1.0 mmol) in anhydrous AcOH (5 mL) was heated at 100 °C for 30–50 h. The progress of the reaction was monitored by TLC (hexane–EtOAc, 2:1; R_f ~0.5–0.6). The solvent was evaporated and the residue was purified by column chromatography (silica gel; hexane–EtOAc, 4:1; R_f ~0.4) and crystallized (hexane).

Table 1 Physical Properties and Elemental Analysis Data for Synthesized Products

Compd	Mp (°C)	IR ($CHCl_3$ or KBr) (cm^{-1})	Found (%)			Formula	Calcd (%)		
			C	H	N		C	H	N
7a	155–156	2984, 2336, 1675, 1640, 1552, 1488, 1400, 1376, 1240, 1192, 1141, 1072, 1040	46.92	3.88	4.67	$C_{12}H_{12}F_3NO_3S$	46.90	3.94	4.56
7b	159–160	3670, 3124, 3058, 3025, 2983, 1717, 1692, 1637, 1495, 1232, 1068, 1041, 970	44.58	4.01	4.28	$C_{12}H_{12}ClF_2NO_3S$	44.52	3.74	3.74
7c	174–175	3060, 2986, 1640, 1552, 1488, 1232, 1120, 1040, 900	41.30	2.92	3.31	$C_{14}H_{12}F_7NO_3S$	41.28	2.97	3.44
9a	144–145	3112, 3060, 1741, 1512, 1444, 1384, 1368, 1352, 1304, 1203, 1159, 1096	46.01	2.25	5.40	$C_{10}H_6F_3NO_2S$	45.98	2.32	5.36
9b	131–132	3944, 3120, 1672, 1649, 1589, 1528, 1450, 1424, 1248, 1196, 979, 824	43.19	2.20	4.98	$C_{10}H_6ClF_2NO_2S$	43.26	2.18	5.04
9c	112–113	3944, 3696, 1744, 1441, 1351, 1232, 1192, 1128, 1064	39.84	2.00	4.00	$C_{12}H_6F_7NO_2S$	39.90	1.67	3.88
13c	126–127	3490, 3051, 1709, 1476, 1425, 1400, 1277, 1204, 1112, 930, 840	43.27	2.90	7.18	$C_{14}H_{11}F_7N_2OS$	43.30	2.86	7.21
14a	194–195	3058, 2988, 1656, 1592, 1528, 1505, 1452, 1428, 1393, 1346, 1304, 1248, 1217, 1187, 1145, 1108, 1012	46.38	2.71	10.84	$C_{10}H_7F_3N_2OS$	46.15	2.71	10.76
14b	191–192	3060, 1712, 1529, 1449, 1424, 1390, 1361, 1320, 1248, 1224, 1144, 1096, 981	43.39	2.58	10.18	$C_{10}H_7ClF_2N_2OS$	43.41	2.55	10.12
14c	192–193	3044, 1744, 1441, 1351, 1232, 1192, 1128, 900, 840	39.98	2.06	7.84	$C_{12}H_7F_7N_2OS$	40.01	1.96	7.78
14d	240–241	3408, 1653, 1557, 1502, 1479, 1444, 1400, 1360, 1302, 1358, 1208, 1184, 1136, 1112, 1096, 992, 912, 827	55.97	2.70	8.76	$C_{15}H_9F_3N_2OS$	55.90	2.81	8.69
17	278–295	2200, 1765, 1643, 1612, 1584, 1576, 1452, 1375, 1296, 1244, 1176, 1138, 1121, 1040	49.63	3.47	17.05	$C_{10}H_8F_3N_3O$	49.39	3.32	17.28
19	304–305	2210, 1656, 1642, 1587, 1576, 1480, 1386, 1310, 1177, 1141, 1110, 1072	53.18	2.76	18.34	$C_{10}H_6F_3N_3$	53.34	2.69	18.66
21a	302–303	2324, 2208, 1776, 1634, 1620, 1587, 1544, 1472, 1425, 1385, 1296, 1244, 1224, 1176, 1138, 1111, 1070, 1004	56.00	2.91	14.98	$C_{13}H_8F_3N_3O$	55.92	2.89	15.05
21e	299–300	2334, 2205, 1696, 1648, 1632, 1588, 1539, 1472, 1387, 1281, 1254, 1212, 1136, 1104, 1071, 1008	52.89	2.64	14.14	$C_{13}H_8ClF_2N_3O$	52.81	2.73	14.21
21h	314–315	2208, 1648, 1632, 1588, 1536, 1488, 1392, 1344, 1284, 1264, 1223, 1180, 1152, 1116, 1072, 1008	47.46	2.05	11.00	$C_{15}H_8F_7N_3O$	47.51	2.13	11.08
22b	131–132	1632, 1572, 1501, 1480, 1427, 1381, 1342, 1320, 1269, 1272, 1256, 1200, 1160, 1134, 1064, 1040, 1016, 939, 827, 744, 691	63.72	3.57	7.88	$C_{19}H_{13}F_3N_2O_2$	63.69	3.66	7.82
22f	129–130	1632, 1568, 1480, 1384, 1344, 1312, 1294, 1264, 1160, 1136, 1072, 1045, 1016, 992, 952, 848, 789, 744, 728, 704	60.91	3.44	7.51	$C_{19}H_{13}ClF_2N_2O_2$	60.89	3.50	7.47
22i	159–160	1632, 1576, 1520, 1437, 1384, 1341, 1288, 1235, 1216, 1184, 1168, 1136, 1112, 1064, 1040, 1000, 852, 728, 704, 680	54.98	2.88	6.05	$C_{21}H_{13}F_7N_2O_2$	55.03	2.86	6.11
23a	239–240	2208, 1648, 1632, 1587, 1540, 1472, 1386, 1298, 1246, 1177, 1138, 1112, 1072	59.28	3.01	15.99	$C_{13}H_6F_3N_3$	59.76	2.32	16.09

Table 1 Physical Properties and Elemental Analysis Data for Synthesized Products (continued)

Compd	Mp (°C)	IR ($CHCl_3$ or KBr) (cm^{-1})	Found (%)			Formula	Calcd (%)		
			C	H	N		C	H	N
23b	144–145	3685, 1712, 1676, 1584, 1480, 1456, 1417, 1400, 1362, 1296, 1224, 1168, 1144, 1120	67.03	3.30	8.23	$C_{19}H_{11}F_3N_2O$	67.06	3.26	8.23
23c	111–112	3096, 1723, 1608, 1560, 1520, 1480, 1456, 1440, 1376, 1304, 1250, 1194, 1168, 1144, 1098, 1062	57.15	3.06	9.50	$C_{14}H_9F_3N_2O_2$	57.15	3.08	9.52
23d	156–157	3060, 2988, 1712, 1627, 1632, 1568, 1552, 1520, 1480, 1456, 1420, 1316, 1260, 1207, 1168, 1147, 1096	65.00	3.84	11.41	$C_{20}H_{14}F_3N_3O$	65.04	3.82	11.38
23e	192–193	3060, 2240, 1512, 1472, 1442, 1360, 1328, 1248, 1220, 1148, 1097, 984	55.80	2.87	15.03	$C_{13}H_6ClF_2N_3$	56.21	2.18	15.14
23f	138–139	3051, 1673, 1600, 1518, 1480, 1449, 1424, 1381, 1284, 1208, 1171, 1144, 1120, 1088, 1088, 992	64.00	3.09	7.83	$C_{19}H_{11}ClF_2N_2O$	63.97	3.11	7.85
23i	164–165	3050, 1674, 1448, 1424, 1384, 1344, 1232, 1216, 1144, 1120, 944	57.25	2.50	6.40	$C_{21}H_{11}F_7N_2O$	57.28	2.52	6.36
26b	228–229	1928, 1684, 1600, 1536, 1488, 1464, 1392, 1372, 1336, 1289, 1251, 1145, 1000, 960, 926, 762, 712, 696	47.03	2.50	6.82	$C_{16}H_{10}F_6N_2O_4$	47.07	2.47	6.86
27	186–185	3060, 1640, 1528, 1480, 1448, 1424, 1368, 1328, 1312, 1269, 1260, 1206, 1156, 1120, 1088, 952	57.10	3.44	7.38	$C_{18}H_{13}F_3N_2O_2S$	57.14	3.46	7.40
29	241–242	1634, 1543, 1496, 1464, 1408, 1304, 1259, 1187, 1160, 1104, 808, 744, 688	49.42	2.28	10.64	$C_{16}H_9F_6N_3O_2$	49.39	2.31	10.76
30a	167–168	3350, 2221, 1637, 1585, 1476, 1346, 1266, 1200, 1185, 1108, 1091	49.43	2.35	10.81	$C_{16}H_9F_6N_3O_2$	49.39	2.31	10.76
30b	186–187	1624, 1582, 1487, 1356, 1312, 1256, 1192, 1138, 1104, 1050, 1024, 984, 920, 881, 800, 752	45.91	1.58	7.17	$C_{15}H_6F_6N_2O_2S$	45.93	1.54	7.14
30c	178–179	1601, 1552, 1480, 1370, 1302, 1216, 1184, 1152, 1107, 984, 865, 768, 744, 712, 688	53.48	2.38	3.01	$C_{21}H_{11}F_6NO_3S$	53.51	2.35	2.97
30d	195–196	1621, 1561, 1476, 1376, 1346, 1263, 1232, 1185, 1144, 1088, 1018, 984, 928, 760, 688	47.29	2.23	2.71	$C_{20}H_{11}F_6NO_4S_2$	47.34	2.19	2.62

Table 2 Selected Physical and Spectral Data of Synthesized Products

Compd (solvent)	Yield (%)	^{19}F NMR [δ (ppm)]	^1H NMR [δ (ppm)]	^{13}C NMR [δ (ppm)]
7a ($CDCl_3$)	58	–77.84 (s)	1.37 (3 H, t, J = 6.7 Hz, CH_3), 2.36 (3 H, s, CH_3), 4.30 (2 H, q, J = 6.7 Hz, CH_2), 6.38 (1 H, d, $J_{10,11}$ = 15.1 Hz, H-10), 6.49 (1 H, s, H-2), 8.39 (1 H, d, $J_{11,10}$ = 15.1 Hz, H-11), 13.12 (1 H, s, NH)	13.7, 14.3, 60.0, 98.0, 106.5, 116.2 (q, J = 270.9 Hz), 118.7, 134.9, 144.5, 150.9, 164.3, 179.0 (q, J = 39.8 Hz)
7b ($CDCl_3$)	84	–67.34 (s)	1.38 (3 H, t, J = 6.7 Hz, CH_3), 2.37 (3 H, s, CH_3), 4.31 (2 H, q, J = 6.7 Hz, CH_2), 6.42 (1 H, d, $J_{10,11}$ = 15.7 Hz, H-10), 6.47 (1 H, s, H-2), 8.38 (1 H, d, $J_{11,10}$ = 15.7 Hz, H-11), 13.11 (1 H, s, NH)	13.7, 14.3, 60.0, 98.0, 104.0, 114.2 (t, J = 304.8 Hz), 119.0, 136.0, 144.5, 160.9, 167.9, 179.01 (t, J = 23.4 Hz)
7c ($CDCl_3$)	87	–80.43 (3 F, t, J = 9.2 Hz), –120.26 (2 F, q, J = 9.2 Hz), –126.44 (2 F, s)	1.39 (3 H, t, J = 7.1 Hz, CH_3), 2.38 (3 H, s, CH_3), 4.31 (2 H, q, J = 7.1 Hz, CH_2), 6.40 (1 H, d, $J_{10,11}$ = 15.1 Hz, H-10), 6.49 (1 H, s, H-2), 8.39 (1 H, d, $J_{11,10}$ = 15.1 Hz, H-11), 12.94 (1 H, s, NH)	13.7, 14.3, 60.9, 92.7, 104.6, 105.3, 137.5, 144.4, 168.1, 168.8, 178.6 (t, J = 27.9 Hz)[a]

Table 2 Selected Physical and Spectral Data of Synthesized Products (continued)

Compd (solvent)	Yield (%)	^{19}F NMR [δ (ppm)]	^{1}H NMR [δ (ppm)]	^{13}C NMR [δ (ppm)]
9a ($CDCl_3$)	46	–79.69 (s)	2.44 (3 H, s, CH_3), 6.80 (1 H, d, $J_{10,11}$ = 7.2 Hz, H-10), 7.08 (1 H, s, H-5), 8.42 (1 H, d, $J_{11,10}$ = 7.2 Hz, H-11)	17.1, 105.5 (q, *J* = 3.4 Hz), 117.9 (q, *J* = 270.9 Hz), 118.7, 123.8, 135.9, 147.6 (q, *J* = 39.8 Hz), 156.5, 157.9
9b ($CDCl_3$)	25	–61.52 (s)	2.43 (3 H, s, CH_3), 6.75 (1 H, d, $J_{10,11}$ = 6.4 Hz, H-10), 7.07 (1 H, s, H-5), 8.43 (1 H, d, $J_{11,10}$ = 6.4 Hz, H-11)	17.1, 105.5 (t, *J* = 3.4 Hz), 118.0 (t, *J* = 304.8 Hz), 119.1, 123.8, 136.0, 147.6 (t, *J* = 23.4 Hz), 154.9, 156.9
9c ($CDCl_3$)	43	–80.98 (3 F, t, *J* = 9.2 Hz), –118.29 (2 F, q, *J* = 9.2 Hz), –126.95 (2 F, s)	2.52 (3 H, s, CH_3), 6.91 (1 H, d, $J_{10,11}$ = 6.3 Hz, H-10), 7.16 (1 H, s, H-5), 8.50 (1 H, d, $J_{11,10}$ = 6.3 Hz, H-11)	17.1, 107.9 (t, *J* = 5.1 Hz), 118.9, 123.7, 135.6, 147.6 (t, *J* = 30.4 Hz), 154.3, 156.4, 157.8[a]
13c ($CDCl_3$)	3	–80.79 (3 F, t, *J* = 8.5 Hz), –115.33 (2 F, q, *J* = 8.5 Hz), –126.94 (2 F, s)	1.47 (3 H, t, *J* = 7.2 Hz, CH_3), 2.46 (3 H, s, CH_3), 4.56 (2 H, q, *J* = 7.2 Hz, CH_2), 6.99 (1 H, s, H-5), 7.31 (1 H, d, $J_{11,10}$ = 7.6 Hz, H-11), 8.72 (1 H, d, $J_{10,11}$ = 7.6 Hz, H-10)	13.3, 16.0, 62.6, 114.3 (t, *J* = 4.7 Hz), 115.6, 118.7, 143.9 (t, *J* = 26.2 Hz), 152.1, 157.4, 158.0[a]
14a ($CDCl_3$)	35	–68.32 (s)	2.55 (3 H, s, CH_3), 7.04 (1 H, s, H-5), 7.20 (1 H, d, $J_{10,11}$ = 7.0 Hz, H-10), 8.22 (1 H, d, $J_{11,10}$ = 7.0 Hz, H-11), 13.41 (1 H, s, NH)	16.8, 111.0, 115.2, 120.4 (q, *J* = 275.6 Hz), 136.1 (q, *J* = 40.3 Hz), 136.4, 152.6, 161.5, 163.2
14b ($CDCl_3$)	74	–57.32 (s)	2.54 (3 H, s, CH_3), 7.03 (1 H, s, H-5), 7.7 (1 H, br d, $J_{10,11}$ = 7.2 Hz, H-10), 8.22 (1 H, br d, $J_{11,10}$ = 7.2 Hz, H-11), 13.30 (1 H, br s, NH)	16.8, 108.4, 115.6, 120.5 (q, *J* = 275.6 Hz), 13.10 (t, *J* = 30.1 Hz), 136.5, 152.6, 161.5, 164.0
14c ($CDCl_3$)	83	–80.63 (3 F, t, *J* = 8.8 Hz), –115.17 (2 F, q, *J* = 8.8 Hz), –126.64 (2 F, s)	2.53 (3 H, s, CH_3), 7.05 (1 H, s, H-5), 7.15 (1 H, br d, $J_{10,11}$ = 7.2 Hz, H-10), 8.30 (1 H, br d, $J_{11,10}$ = 7.2 Hz, H-11), 13.45 (1 H, br s, NH)	16.6, 112.6, 115.3, 136.1, 142.8 (m) 152.7, 161.2, 163.0[a]
14d ($CDCl_3$)	58	–68.41 (s)	7.17 (1 H, br d, $J_{10,11}$ = 7.2 Hz, H-10), 7.45 (3 H, m, H-14, H-15, H-16), 7.65 (1 H, s, H-5), 7.93 (2 H, m, H-13, H-17), 8.46 (1 H, br d, $J_{11,10}$ = 7.6 Hz, H-11)	110.4, 114.2, 115.9, 118.5 (q, *J* = 245.7 Hz), 118.5, 126.5, 128.9 (q, *J* = 31.0 Hz), 129.0, 133.0, 136.7, 155.3, 161.2
17 ($CDCl_3$)	64	–74.58 (s)	2.36 (3 H, s, CH_3), 6.41 (1 H, d, $J_{8,7}$ = 15.0 Hz, H-8), 6.47 (1 H, s, H-4), 8.39 (1 H, d, $J_{7,8}$ = 15.0 Hz, H-7), 13.04 (2 H, br s, NH)	16.0, 74.5, 106.2, 110.0 (br m), 115.8, 121.0 (q, *J* = 292.2 Hz), 127.7, 137.2, 154.0, 174.1 (q, *J* = 35.0 Hz)
19 ($CDCl_3$)	42	–65.48 (s)	2.38 (3 H, s, CH_3), 6.97 (1 H, s, H-5), 7.82 (1 H, d, $J_{8,7}$ = 7.3 Hz, H-8), 8.07 (1 H, d, $J_{7,8}$ = 7.3 Hz, H-7)	13.2, 95.4, 106.7 (q, *J* = 4.7 Hz), 116.5 (q, *J* = 275.8 Hz), 116.8, 123.2, 125.0 (q, *J* = 37.8 Hz), 131.4, 134.0, 149.0
21a (DMSO-d_6)	91	–75.97 (s)	5.89 (1 H, d, $J_{11,12}$ = 13.3 Hz, H-11), 7.33 (2 H, m, H-6, H-9), 7.43 (2 H, m, H-7, H-8), 8.42 (1 H, d, $J_{12,11}$ = 13.3 Hz, H-13), 13.67 (2 H, br s, H-3, H-1)	67.8, 97.6, 111.8, 117.3, 117.89 (q, *J* = 292.2 Hz), 124.0, 131.5, 147.1, 150.3, 173.1 (q, *J* = 31.3 Hz)
21e (DMSO-d_6)	95	–63.49 (s)	5.87 (1 H, d, $J_{11,12}$ = 13.1 Hz, H-11), 7.29 (2 H, m, H-7, H-8), 7.43 (2 H, m, H-6, H-9), 8.36 (1 H, d, $J_{12,11}$ = 13.1 Hz, H-12), 13.56 (1 H, br s, H-3, H-1)	68.0, 96.9, 112.3, 117.9, 122.5 (t, *J* = 304.6 Hz), 124.5, 132.4, 147.8, 150.7, 176.2 (t, *J* = 23.4 Hz)
21h (DMSO-d_6)	93	–80.69 (3 F, t, *J* = 8.2 Hz), –120.40 (2 F br m), –126.64 (2 F, br s)	5.93 (1 H, d, $J_{11,12}$ = 13.2 Hz, H-11), 7.44 (2 H, m, H-6 H-9), 7.29 (2 H, m, H-7, H-8), 8.40 (1 H, d, $J_{12,11}$ = 13.2 Hz, H-12), 13.64 (2 H, br s, H-3, H-1)	68.9, 99.1, 112.3, 117.7, 124.5, 132.0, 147.3, 150.7, 174.7 (t, *J* = 22.80 Hz)[a]
22b ($CDCl_3$)	76	–83.69 (s)	4.99 (1 H, d, $J_{3,4}$ = 10.0 Hz, H-3), 6.80 (1 H, d, $J_{4,3}$ = 10.0 Hz, H-4), 7.24 (2 H, m, H-11, H-12), 7.49 (5 H, s, H-22, H-23, H-24, H-25, H-26), 7.72 (1 H, m, H-13), 7.83 (1 H, m, H-10), 8.86 (1 H, s, OH), 13.25 (1 H, s, NH)	78.2, 88.9 (q, *J* = 39.3 Hz), 90.6, 105.2, 113.6, 115.3, 122.9, 124.0, 128.1, 128.2, 129.7, 129.8, 129.9 (q, *J* = 272.5 Hz), 138.6, 149.5, 180.7

Table 2 Selected Physical and Spectral Data of Synthesized Products (continued)

Compd (solvent)	Yield (%)	^{19}F NMR [δ (ppm)]	^{1}H NMR [δ (ppm)]	^{13}C NMR [δ (ppm)]
22f ($CDCl_3$)	83	–65.53 (s)	5.23 (1 H, d, $J_{3,4}$ = 10.4 Hz, H-3), 6.86 (1 H, d, $J_{4,3}$ = 10.4 Hz, H-4), 7.31 (2 H, m, H-11, H-12), 7.44 (3 H, m, H-22, H-24, H-26), 7.53 (2 H, m, H-25, H-23), 7.07 (1 H, m, H-13), 7.85 (1 H, m, H-10), 8.00 (1 H, s, OH), 13.17 (1 H, br s, NH)	78.2, 88.9 (t, J = 26.1 Hz), 90.6, 105.2, 113.6, 115.3, 122.9, 124.0, 128.1, 128.2, 129.7, 129.8, 129.9 (t, J = 309.0 Hz), 138.6, 149.5, 180.7
22i ($CDCl_3$)	43	–80.80 (3 F, t, J = 8.2 Hz), –119.00 (2 F, br m), –123.96 (2 F, br s)	4.95 (1 H, d, $J_{3,4}$ = 10.1 Hz, H-3), 6.78 (1 H, d, $J_{4,3}$ = 10.1 Hz, H-4), 7.29 (2 H, m, H-11, H-12), 7.47 (5 H, s, H-22, H-23, H-24, H-25, H-26), 7.70 (1 H, m, H-13), 7.84 (1 H, m, H-10), 9.06 (1 H, s, OH), 13.21 (1 H, br s, NH)	88.0, 88.8, 90.6, 101.7, 113.2, 115.4, 123.3, 124.7, 128.2, 128.6, 129.7, 130.0, 130.4, 131.9, 140.5, 148.2, 174.8 (t, J = 27.9 Hz)[a]
23a ($CDCl_3$)	85	–65.24 (s)	7.57 (1 H, m, H-6), 7.69 (2 H, m, H-8, H-7), 8.04 (1 H, d, $J_{11,12}$ = 7.8 Hz, H-11), 8.09 (1 H, d, $J_{12,11}$ = 7.8 Hz, H-12), 8.33 (1 H, d, $J_{9,8}$ = 7.3 Hz, H-9)	106.4, 112.0, 114.6, 115.1, 120.3 (q, J = 271.8 Hz), 121.0, 124.2, 127.4, 127.8, 129.7 (q, J = 36.2 Hz), 136.6, 144.6, 146.4
23b ($CDCl_3$)	94	–65.70 (s)	7.47 (4 H, m, H-Ar), 7.59 (3 H, m, H-Ar), 7.94 (2 H, m, H-6, H-11), 8.00 (1 H, d, $J_{12,11}$ = 8.1 Hz, H-12), 8.18 (1 H, d, $J_{9,8}$ = 8.6 Hz, H-9)	110.0 (q, J = 6.6 Hz), 114.2 (q, J = 6.6 Hz), 120.5 (q, J = 273.2 Hz), 123.3, 126.4, 126.5, 127.4, 128.6 (q, J = 36.8 Hz), 128.6, 133.0, 134.2, 136.0, 145.0 146.1 192.4
23c ($CDCl_3$)	56	–65.86 (s)	4.01 (3 H, s, CH_3), 7.35 (1 H, d, $J_{11,12}$ = 7.8 Hz, H-11), 7.51 (1 H, m, H-8), 7.62 (1 H, m, H-7), 7.95 (1 H, d, $J_{12,11}$ = 7.8 Hz, H-12), 8.44 (1 H, d, $J_{6,7}$ = 7.3 Hz, H-6), 9.43 (1 H, d, $J_{9,8}$ = 7.3 Hz, H-9)	53.0, 106.4, 111.9, 114.6, 115.1, 120.0 (q, J = 271.8 Hz), 124.3, 127.4, 127.8, 129.7 (q, J = 36.2 Hz), 137.0, 144.0, 146.5, 160.5
23d ($CDCl_3$)	76	–65.32 (s)	4.86 (2 H, d, J = 6.1 Hz, CH_2), 7.34 (3 H, m, H-Ar), 7.49 (4 H, m, H-Ar), 7.62 (1 H, m, H-8), 7.96 (1 H, d, $J_{12,11}$ = 7.4 Hz, H-12), 8.16 (1 H, br d, $J_{6,7}$ = 8.8 Hz, H-6), 8.57 (1 H, d, $J_{11,12}$ = 7.4 Hz, H-11), 11.13 (1 H, br s, NH)	43.9, 111.3 (q, J = 7.8 Hz), 114.5 (q, J = 7.8 Hz), 120.3, 120.5 (q, J = 272.9 Hz), 124.8, 126.8, 127.4, 127.5, 128.7 (q, J = 35.3 Hz), 129.1, 130.4, 138.3, 143.5, 146.6, 162.1
23e ($CDCl_3$)	79	–51.64 (s)	7.16 (1 H, m, H-9), 7.53 (1 H, m, H-8), 7.65 (1 H, m, H-7), 7.99 (1 H, d, $J_{12,11}$ = 7.7 Hz, H-12), 8.07 (1 H, d, $J_{11,12}$ = 7.7 Hz, H-11), 8.78 (1 H, d, $J_{6,7}$ = 6.1 Hz, H-6)	99.4 (t, J = 3.5 Hz), 105.3 (t, J = 5.4 Hz), 111.1, 111.7, 121.2, 123.1 (t, J = 28.3 Hz), 123.9, 127.9, 128.5, 129.5, 141.4 (t, J = 28.3 Hz), 144.5, 145.3
23f ($CDCl_3$)	83	–53.56 (s)	7.47 (4 H, m, H-Ar), 7.59 (3 H, m, H-Ar), 7.65 (1 H, m, H-Ar), 7.94 (2 H, m, H-Ar), 8.00 (1 H, d, $J_{12,11}$ = 7.8 Hz, H-12), 8.18 (1 H, d, $J_{11,12}$ = 7.8 Hz, H-11)	109.2 (t, J = 8.0 Hz), 115.9 (t, J = 7.6 Hz), 121.5 (t, J = 288.2 Hz), 123.1, 126.3, 126.6, 127.5, 128.6, 130.4, 132.5, 133.9 (t, J = 33.7 Hz), 134.2, 136.0, 145.1, 146.3, 192.4
23i ($CDCl_3$)	73	–80.13 (3 F, t, J = 8.8 Hz), –107.44 (2 F, q, J = 8.8 Hz), –123.33 (2 F, s)	7.44 (4 H, m, H-Ar), 7.59 (3 H, m, H-Ar), 7.94 (2 H, m, H-6, H-11), 8.00 (1 H, d, $J_{12,11}$ = 8.1 Hz, H-12), 8.09 (1 H, d, $J_{9,8}$ = 8.6 Hz, H-9)	113.7 (t, J = 9.7 Hz), 115.1 (t, J = 11.5 Hz), 121.2, 123.2, 125.8, 126.3, 128.1 (t, J = 32.2 Hz), 128.2, 128.7, 133.6, 132.5, 134.2, 135.9, 145.0, 146.5, 192.3[a]
26b (DMSO-d_6)	95	–66.88 (3 F, s), –80.58 (3 F, s)	3.57 (3 H, s, CH_3), 7.15 (2 H, m, H-11, H-12), 7.45 (1 H, d, $J_{10,11}$ = 7.8 Hz, H-10), 7.73 (1 H, d, $J_{13,12}$ = 7.5 Hz, H-13), 9.04 (1 H, s, H-4), 9.05 (1 H, s, NH), 12.94 (1 H, s, OH)	52.0, 89.0, 89.3 (q, J = 35.0 Hz), 97.4, 116.8 (q, J = 2.3 Hz), 118.3 (q, J = 290.1 Hz), 125.6 (q, J = 296.7 Hz), 125.7, 126.5, 130.4, 131.7, 144.6 (q, J = 2.4 Hz), 146.7, 164.9, 176.4 (q, J = 33.2 Hz)
27 (DMSO-d_6)	84	–66.02 (s)	7.52 (6 H, m, H-7, H-8, H-12, H-23, H-24, H-25), 8.09 (2 H, m, H-6, H-11), 8.39 (3 H, m, H-9, H-22, H-26)	109.4 (q, J = 6.1 Hz), 114.0 (q, J = 6.1 Hz), 119.9 (q, J = 272.6 Hz), 121.4, 123.6, 126.6, 127.2, 128.6, 129.1, 129.5, 131.0 (q, J = 36.1 Hz), 133.2, 133.9, 138.7, 144.7
29 (DMSO-d_6)	56	–70.91 (s)	3.71 (3 H, s, CH_3), 5.70 (1 H, d, $J_{9,8}$ = 13.0 Hz, H-9), 7.13 (2 H, m, H-12, H-8), 7.23 (1 H, m, H-7), 7.42 (1 H, s, NH), 8.08 (1 H, d, $J_{6,7}$ = 13.6 Hz, H-6)	32.1, 67.5, 98.3, 111.0, 112,1, 118.0, 118.5 (q, J = 296.3 Hz), 124.3, 125.1, 130.8, 133.6, 149.5, 149.9, 174.1 (q, J = 32.4 Hz)

Table 2 Selected Physical and Spectral Data of Synthesized Products (continued)

Compd (solvent)	Yield (%)	^{19}F NMR [δ (ppm)]	^{1}H NMR [δ (ppm)]	^{13}C NMR [δ (ppm)]
30a (DMSO-d_6)	84	–67.13 (3 F, s), –80.18 (3 F, s)	3.83 (3 H, s, CH_3), 7.23 (2 H, m, H-12, H-11), 7.50 (1 H, s, H-4), 7.55 (1 H, d, $J_{10,11}$ = 8.1 Hz, H-10), 7.77 (1 H, d, $J_{13,12}$ = 8.1 Hz, H-13), 9.23 (1 H, s, OH)	36.3, 79.6, 85.6 (q, J = 34.9 Hz), 104.0, 120.0 (q, J = 292.1 Hz), 120.7, 124.0, 126.3 (q, J = 296.7 Hz), 127.0, 127.9, 129.6, 142.0, 143.9, 169.3, 178.1 (q, J = 38.0 Hz)
30b (DMSO-d_6)	87	–69.27 (3 F, s), –85.22 (3 F, s)	7.48 (1 H, m, H-12), 7.57 (1 H, m, H-11), 7.92 (1 H, s, H-7), 8.03 (1 H, d, $J_{10,11}$ = 8.7 Hz, H-10), 8.39 (1 H, d, $J_{13,12}$ = 8.7 Hz, H-13), 9.07 (1 H, s, OH)	78.6, 89.3 (q, J = 35.0 Hz), 103.4, 119.0 (q, J = 291.0 Hz), 120.9, 124.6, 125.6 (q, J = 296.8 Hz), 126.9, 127.9, 129.7, 141.5, 144.4 (q, J = 2.3 Hz), 165.3, 176.4 (q, J = 34.0 Hz)
30c (DMSO-d_6)	85	–69.20 (3 F, s), –84.78 (3 F, s)	7.56 (7 H, m, H-12, H-11, H-30, H-29, H-28, H-31, H-27), 7.84 (1 H, d, $J_{13,12}$ = 8.2 Hz, H-13), 8.16 (1 H, s, H-7), 8.61 (1 H, d, $J_{10,11}$ = 8.8 Hz, H-10), 9.30 (1 H, s, OH)	91.5 (q, J = 34.4 Hz), 103.5, 106.0, 119.1 (q, J = 287.9 Hz), 120.4, 121.0 (q, J = 297.3 Hz), 121.3, 122.6, 128.5, 129.0, 129.2, 129.4, 130.6, 137.2, 138.7, 145.4, 182.4 (q, J = 29.3 Hz), 190.0
30d (DMSO-d_6)	91	–68.21 (3 F, s), –87.04 (3 F, s)	7.51 (5 H, m, H-12, H-11, H-30, H-29, H-28), 7.71 (1 H, d, $J_{13,12}$ = 7.9 Hz, H-13), 7.91 (2 H, m, H-31, H-27), 8.22 (1 H, s, H-7), 8.51 (1 H, d, $J_{10,11}$ = 8.7 Hz, H-10), 9.26 (1 H, s, OH)	82.9 (q, J = 34.4 Hz), 100.6, 106.0, 117.1 (q, J = 287.9 Hz), 120.4, 120.9 (q, J = 295.0 Hz), 122.6, 128.5, 129.0, 129.2, 129.4, 132.9, 134.6, 138.8, 146.4, 162.5, 180.4 (q, J = 29.3 Hz)

[a] Signals arising from the carbon atoms of the C_3F_7 group are overlapping multiplets.

Synthesis of Pyridones 14a–d; General Procedure

A mixture of 1,3-thiazol-2-ylacetonitrile **10a**,**10b** (1.0 mmol) and enone **3a–c** (1.0 mmol) in anhydrous AcOH (10 mL) was stirred at r.t. for 10–15 h. The progress of the reaction was monitored by ^{19}F NMR spectroscopy. The solvent was evaporated and the residue was crystallized (CCl_4).

(2*E*,3*E*)-6,6,6-Trifluoro-2-(4-methyl-1,3-dihydro-2*H*-imidazol-2-ylidene)-5-oxohex-3-enenitrile (17)

A mixture of imidazole **16** (1.0 mmol) and enone **3a** (168 mg, 1.0 mmol) in HMPA (5 mL) was stirred at r.t. for 10 h. The progress of the reaction was monitored by ^{19}F NMR spectroscopy. The reaction mixture was quenched with H_2O (15 mL) and the precipitated solid was collected by filtration, dried under vacuum, and crystallized ($CHCl_3$–hexane, 1:10).

Preparation of 3-Methyl-5-(trifluoromethyl)imidazo[1,2-*a*]pyridine-8-carbonitrile (19)

A mixture of imidazole **16** (1.0 mmol) and enone **3a** (168 mg, 1.0 mmol) in HMPA (5 mL) was heated at 100 °C for 7 h. The progress of the reaction was monitored by ^{19}F NMR spectroscopy. The reaction mixture was quenched with H_2O (15 mL) and the precipitated solid was collected by filtration, dried under vacuum, and crystallized (CCl_4).

Synthesis of 21a, 21e and 21h; General Procedure

The β-alkoxyvinyl polyfluoroalkyl ketone **3a–c** (1.0 mmol) was added to a solution of 1*H*-benzimidazol-2-ylacetonitrile (**20a**; 157 mg, 1.0 mmol) in anhydrous MeCN (5 mL) and the mixture was stirred at r.t. for 1–2 h. The solvent was carefully evaporated without extra heating and the residue was crystallized (MeCN–$CHCl_3$, 5:1).

Synthesis of 22b, 22h and 22; General Procedure

The β-alkoxyvinyl polyfluoroalkyl ketone **3a–c** (1.0 mmol) was added to a solution of 2-(1*H*-benzimidazol-2-yl)-1-phenylethanone (**20c**; 236 mg, 1.0 mmol) in anhydrous MeCN (5 mL). The mixture was stirred at r.t. for 6–8 h. The solvent was carefully evaporated under vacuum without extra heating and the residue was crystallized (CCl_4–$CHCl_3$, 10:3).

Synthesis of 23a–d; General Procedure (Method 1)

A mixture of 2-substituted benzimidazole **20** (1.0 mmol) and β-alkoxyvinyl polyfluoroalkyl ketone **3a** (168 mg, 1.0 mmol) was refluxed in anhydrous toluene (10 mL) for 6–12 h. The solvent was carefully evaporated and the residue was crystallized (CCl_4–hexane).

Synthesis of 23e–i; General Procedure (Method 2)

A mixture of 2-substituted benzimidazole **20** (1.0 mmol) and β-alkoxyvinyl polyfluoroalkyl ketone **3a–c** or product **21a**, **21e**, **22b**, **22f**, **22i** (1.0 mmol) was stirred in anhydrous MeCN (5 mL) at 40 °C for 12–24 h. The progress of the reaction was monitored by TLC (EtOAc–hexane, 1:2; R_f ~0.3–0.4). The reaction mixture was quenched with H_2O (15 mL) and the precipitated solid was collected by filtration, dried under vacuum and crystallized ($CHCl_3$–hexane).

Methyl 1-Hydroxy-2-(trifluoroacetyl)-1-(trifluoromethyl)-1,5-dihydropyrido[1,2-*a*]benzimidazole-4-carboxylate (26b)

Methyl 1*H*-benzimidazol-2-ylacetate (**20b**; 190 mg, 1.0 mmol) and 1,1,1,5,5,5-hexafluoro-3-(isobutoxymethylene)pentane-2,4-dione (**24**; 292 mg 1.0 mmol) was stirred in anhydrous MeCN (5 mL) at r.t. for 6–12 h. The progress of the reaction was monitored by TLC (EtOAc–hexane, 1:2; R_f = 0.3). The reaction mixture was quenched with H_2O (15 mL) and the precipitated solid was collected by filtration, dried under vacuum and crystallized ($CHCl_3$).

4-(Phenylsulfonyl)-1-(trifluoromethyl)pyrido[1,2-*a*]benzimidazole (27)

2-[(Phenylsulfonyl)methyl]-1*H*-benzimidazole (**25**; 272 mg, 1.0 mmol) and 1,1,1,5,5,5-hexafluoro-3-(isobutoxymethylene)pentane-2,4-dione (**24**; 292 mg, 1.0 mmol) was stirred in anhydrous MeCN (5 mL) at r.t. for 10 h. The progress of the reaction was monitored by TLC (EtOAc–hexane, 1:2; R_f = 0.4). The reaction mixture was quenched with H_2O (45 mL) and the precipitated solid was collected by filtration, dried under vacuum and crystallized (toluene).

(2*Z*)-6,6,6-Trifluoro-2-(1-methyl-1,3-dihydro-2*H*-benzimidazol-2-ylidene)-5-oxo-4-(trifluoroacetyl)hex-3-enenitrile (29a)
A mixture of (1-methyl-1*H*-benzimidazol-2-yl)acetonitrile (**28a**; 171 mg, 1.0 mmol) and 1,1,1,5,5,5-hexafluoro-3-(isobutoxymethylene)pentane-2,4-dione (**24**; 292 mg, 1.0 mmol) was stirred in anhydrous HMPA (6 mL) at 10 °C for 3 h. The progress of the reaction was monitored by TLC (EtOAc–hexane, 1:2; R_f = 0.3). The reaction mixture was quenched with H_2O (25 mL) and the precipitated solid was collected by filtration, dried under vacuum and crystallized (CCl_4–hexane, 1:2).

1-Hydroxy-5-methyl-2-(trifluoroacetyl)-1-(trifluoromethyl)-1,5-dihydropyrido[1,2-*a*]benzimidazole-4-carbonitrile (30a)
A mixture of (1-methyl-1*H*-benzimidazol-2-yl)acetonitrile (**28a**; 171mg 1.0 mmol) and 1,1,1,5,5,5-hexafluoro-3-(isobutoxymethylene)pentane-2,4-dione (**24**; 292 mg, 1.0 mmol) was stirred in anhydrous MeCN (10 mL) at 45 °C for 6 h. The progress of the reaction was monitored by TLC (EtOAc–hexane, 1:2, R_f = 0.4). The reaction mixture was quenched with H_2O (25 mL) and the precipitated solid was collected by filtration, dried under vacuum and crystallized ($CHCl_3$).

Synthesis of 30b–d; General Procedure
A mixture of benzthiazole **28** (1.0 mmol) and 1,1,1,5,5,5-hexafluoro-3-(isobutoxymethylene)pentane-2,4-dione (**24**; 292 mg, 1.0 mmol) was stirred in anhydrous MeCN (15 mL) at r.t. for 2–6 h. The progress of the reaction was monitored by TLC (EtOAc–hexane, 1:2; R_f = 0.3). The reaction mixture was quenched with H_2O (45 mL) and the precipitated solid was collected by filtration, dried under vacuum, and crystallized ($CHCl_3$).

Crystallographic data (excluding structure factors) for the reported structure have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-651853. Copies of the data can be obtained free of charge on application to The Director CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(1223)336033, email:deposit@ccdc.cam.ac.uk].

Acknowledgment

We are grateful to Enamine Ltd. (Kiev) for recording the NMR spectra and for the supply of materials. The X-ray diffraction analysis by Mrs S.V. Shishkina and Dr O.V. Shishkin (STC 'Institute for Single Crystals', Kharkov) is gratefully acknowledged.

References

(1) *Organofluorine Compounds in Medicinal Chemistry and Biochemical Applications*; Filler, R.; Kobayashi, Y.; Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, **1993**, .
(2) Sata, N.; Shibata, T.; Jitsuoka, M.; Ohno, T.; Takahashi, T.; Hirohashi, T.; Kanno, T.; Iwaasa, H.; Kanatani, A.; Fukami, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1761.
(3) Carlsson, C.; Rosen, I.; Nilsson, E. *Acta Anaesthesiol. Scand.* **1993**, *27*, 87.
(4) Kelly, T.; Bell, S.; Osashi, N.; Armstrong-Chong, J. *J. Am. Chem. Soc.* **1988**, *110*, 6471.
(5) (a) Cox, R.; O'Hagan, D. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2537. (b) Rigby, J.; Balasubramanian, N. *J. Org. Chem.* **1989**, *54*, 224.
(6) Williams, D.; Lowder, P.; Gu, Y.-G. *Tetrahedron Lett.* **1997**, *38*, 327.
(7) Teshima, Y.; Shin-ya, K.; Shimazu, A.; Furihota, K.; Chul, H. S.; Furihata, K.; Hayakawa, Y.; Nagai, K.; Seto, H. *J. Antibiot.* **1991**, *44*, 685.
(8) Matyus, P.; Kasztreiner, E.; Diesler, E.; Behr, A.; Varga, I.; Kosary, J.; Rabloczky, G.; Jaszlits, L. *Arch. Pharm.* **1994**, *327*, 543.
(9) Narusevicius, E.; Garaliene, V.; Krauze, A.; Duburs, G. *Khim.-Farm. Zh.* **1989**, *23*, 1459.
(10) Nino, A.; Munoz-Caro, C.; Carbo-Dorca, R.; Girones, X. *Biophys. Chem.* **2003**, *104*, 417.
(11) (a) Gerus, I. I.; Gorbunova, M. G.; Kukhar, V. P. *J. Fluorine Chem.* **1994**, *69*, 195. (b) Gorbunova, M. G.; Gerus, I. I.; Kukhar, V. P. *Synthesis* **2000**, 738.
(12) Gerus, I. I.; Vdovenko, S. I.; Gorbunova, M. G.; Kukhar, V. P. *Khim. Geterotsikl. Soedin.* **1991**, 502; *Chem. Abstr.* **1991**, *115*, 1832349.
(13) Kacharova, L. M.; Gerus, I. I.; Kacharov, A. D. *J. Fluorine Chem.* **2002**, *117*, 193.
(14) Gerus, I. I.; Gorbunova, M. G.; Vdovenko, S. I.; Yagupolskii, Yu. L.; Kukhar, V. P. *Zh. Org. Khim.* **1990**, *26*, 1877; *Chem. Abstr.* **1991**, *115*, 8196g.
(15) Gerus, I. I.; Tolmachova, N. A.; Vdovenko, S. I.; Fröhlich, R.; Haufe, G. *Synthesis* **2005**, 1269.
(16) Tolmachova, N. A.; Gerus, I. I.; Vdovenko, S. I.; Essers, M.; Fröhlich, R.; Haufe, G. *Eur. J. Org. Chem.* **2006**, 4704.
(17) Volovenko, Y. M.; Nemasanyii, A. G.; Ryabokon, I. G.; Babichev, F. S. *Ukr. Khim. Zh.* **1988**, *54*, 295.
(18) Shaozhong, W.; Tan, T.; Jianxin, L.; Hongwen, H. *Synlett* **2005**, 2658.
(19) Pazenok, S. V.; Gerus, I. I.; Chaika, E. A.; Yagupolskii, L. M. *J. Org. Chem. USSR (Engl. Transl.)* **1989**, *25*, 1238.
(20) Hojo, R.; Masuda, M.; Okana, E. *Synthesis* **1990**, 347.